Appendix A (Marked up pages 1-5)

Acylated Cyclodextrin : Guest Molecule Inclusion Complexes

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application Serial Nos. 60/203,500, filed May 11, 2000 and 60/205,715, filed May 19, 2000, which are all herein incorporated by reference in their entireties.

Field of Invention

This invention relates to a novel process for the preparation of inclusion complexes comprising acylated cyclodextrin host molecules and guest molecules, a novel process for the preparation of carrier polymer and acylated cyclodextrin:guest molecule inclusion complex composites by melt compounding, novel inclusion complexes comprising acylated cyclodextrins host molecules and guest molecules, novel composites comprising a carrier polymer and an acylated cyclodextrin:guest molecule inclusion complex, shaped articles comprising a carrier polymer and an acylated cyclodextrin:guest molecule inclusion complex capable of the sustained release of guest molecules, and medical devices comprising a carrier polymer and an acylated cyclodextrin:pharmaceutical active inclusion complex capable of the sustained release of guest molecules.

BACKGROUND

Cyclodextrins (CDs) are cyclic oligomers of glucose which typically contain 6, 7, or 8 glucose monomers joined by α-1,4 linkages. These oligomers are commonly called α-CD, β-CD, and γ-CD, respectively. Higher oligomers containing up to 12 glucose monomers are known but their preparation is more difficult. Each glucose unit has three hydroxyls available at the 2, 3, and 6 positions. Hence, α-CD has 18 hydroxyls or 18 substitution sites available and can have a maximum degree of substitution (DS) of 18. Similarly, β-CD and γ-CD have a maximum DS of 21 and 24 respectively. The DS is often expressed as the average DS, which is the number of substituents divided by the number of glucose monomers in the cyclodextrin. For

example, a fully acylated β-CD would have a DS of 21 or an average DS of 3. In terms of nomenclature, this derivative is named heptakis(2,3,6-tri-O-acetyl)-β-cyclodextrin which is typically shortened to triacetyl-β-cyclodextrin.

The production of CD involves first treating starch with an α-amylase to partially lower the molecular weight of the starch followed by treatment with an enzyme known as cyclodextrin glucosyl transferase which forms the cyclic structure. By conducting the reaction in the presence of selected organic compounds, eg. toluene, crystalline CD complexes are formed which facilitate isolation of CD with predetermined ring size.

Topologically, CD can be represented as a toroid in which the primary hydroxyls are located on the smaller circumference and the secondary hydroxyls are located on the larger circumference. Because of this arrangement, the interior of the torus is hydrophobic while the exterior is sufficiently hydrophilic to allow the CD to be dissolved in water. This difference between the interior and exterior faces allows the CD or selected CD derivatives to act as a host molecule and to form inclusion complexes with hydrophobic guest molecules provided the guest molecule is of the proper size to fit in the cavity. The CD inclusion complex can then be dissolved in water thereby providing for the introduction of insoluble or sparingly soluble guest molecule into an aqueous environment. This property makes CDs and water soluble CD derivatives particularly useful in the pharmaceutical, cosmetic, and food industries.

Recently, there has been some interest in the development of CD derivatives which could serve as host molecules for hydrophilic guest molecules. The primary interest has been for the sustained release of water soluble drugs. Acylated cyclodextrin derivatives, such as heptakis(2,3,6-tri-O-acetyl)-β-cyclodextrin (Uekama, et al., J. Pharm. Pharmacol. 1994, 46, 714-717), have been proposed as CD derivative host molecules.

In yet another study (Chem. Pharm. Bull. 1995, 43, 130-136), Uekama et al., reported on the preparation and characterization of acylated-β-CDs as a sustained release carrier of different water soluble drugs. The drugs investigated were molsidomine, isosorbide dinitrate, propranolol hydrochloride, and salbutamol sulfate. In still yet another study (Pharm. Sci. 1996, 2, 533-536), Uekama et al., investigated the controlled release of diltiazem from a combination of short and long chain acylated-β-CDs in dogs.

U.S. Patent No. 5,904,929, to Uekama et al., discloses that a sheet-like or film-like pharmaceutical composition for transmucosal or transdermal administration can be prepared by adding a solution or suspension of C2-C18 acylated cyclodextrins and a drug in an organic solvent onto a backing membrane selected from aluminum foil, polyethylene terephthalate film, or polystyrene film followed by solvent removal. Various drugs are disclosed in this reference, and the preferred peracylated cyclodextrins are the C4-C6 peracylated-β-CD.

SUMMARY OF INVENTION

The present invention is directed to a method of making an inclusion complex comprising an acylated cyclodextrin host molecule and a guest molecule, wherein the method comprises the steps of: a)contacting the acylated cyclodextrin host molecule and the guest molecule to form an inclusion complex; and b) precipitating the inclusion complex in an aqueous medium.

The present invention is further directed to an inclusion complex comprising an acylated cyclodextrin host molecule and a guest molecule, wherein the guest molecule comprises from about 5 % (wt.) to about 15 % (wt.) of the inclusion complex.

The present invention is in other embodiments related to various inclusion complexes.

Moreover, the present invention relates to a composition comprising a polymer and an inclusion complex, wherein the inclusion complex comprises an acylated cyclodextrin host molecule and a guest molecule. In addition the invention is directed at composites and articles comprising such a composition.

The present invention also is related to a method of making a composition comprising a polymer and an inclusion complex comprised of an acylated cyclodextrin host molecule and a guest molecule, wherein the method comprises: a) contacting the polymer, the acylated cyclodextrin host molecule and the guest molecule to form a polymer/inclusion complex mixture; and b) precipitating the mixture in an aqueous medium.

Additionally, the present invention is related to a method of making a composition comprising a polymer and an inclusion complex comprised of an acylated cyclodextrin host molecule and a guest molecule, wherein the method comprises: a) contacting the polymer, the acylated cyclodextrin host molecule and the guest molecule to form a mixture; and b) melt compounding the mixture to form the composition comprising the polymer and the inclusion complex.

The present invention is further related to a method of making a composition comprising a polymer and an inclusion complex comprised of an acylated cyclodextrin host molecule and a guest molecule, wherein the method comprises: a) contacting the acylated cyclodextrin host molecule and the guest molecule to form an inclusion complex; b) precipitating the inclusion complex in an aqueous medium; c) purifying the inclusion complex to substantially remove the water and any organic solvent; d) contacting the polymer with the purified inclusion complex to form a mixture; and e) melt compounding the mixture to form the composition comprising the polymer and the inclusion complex

Furthermore, the present invention relates to a medical device or a solid pharmaceutical composition comprising a polymer and an inclusion complex, wherein the inclusion complex comprises an acylated cyclodextrin host molecule and a pharmaceutical active guest molecule.

The present invention also relates to a method of making a solid pharmaceutical composition comprising a polymer and an inclusion complex, wherein the inclusion complex comprises an acylated cyclodextrin host molecule and a pharmaceutical active guest molecule, wherein the method comprises:
a) contacting the acylated cyclodextrin host molecule and the pharmaceutical active guest molecule to form an inclusion complex; b) precipitating the inclusion complex in an aqueous medium; c) purifying the inclusion complex to substantially remove the water and any organic solvent; d) contacting the polymer with the purified inclusion complex to form a mixture; and e) melt compounding the mixture to form the composition comprising the polymer and the inclusion complex.

Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides the chemical structure of Prostaglandin E_1 (PGE_1).

Figure 2 shows the degradation processes of PGE_1.